#14
B. Webb
6/22/01

Attorney's Docket No. 9250-22

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Goudsmit, et al.
Serial No: 09/463,352 Group Art Unit: 1655
Filed: 21 January 2000 Examiner: B. Sisson
For: *NUCLEIC ACID SEQUENCES THAT CAN BE USED AS PRIMERS AND PROBES IN THE AMPLICATION AND DETECTION OF ALL SUBTYPES OF HIV-1*

June 13, 2001

Commissioner for Patents
Washington, DC 20231

RESPONSE

This is in response to the Official Action of February 14, 2001.

Remarks

This is in response to the Official Action mailed February 14, 2001.

Claims 1-9, 11 and 12 stand rejected as obvious over **Montagnier et al**. in view of **Research Genetics**. For the reasons set forth below, this rejection is respectfully traversed.

In the Official Action, it is indicated that **Montagnier** teach that primers may be found in the LTR, and that the LTR is the region from which applicant has selected the instantly claimed primers/probes. It is noted that **Research Genetics** through their advertisement disclose software that is said to allow the selection of primers. In view of these two references, it is concluded that the claimed invention is obvious. However, the Official Action does not show how the references may be combined to teach primers having the particular sequences recited in the claims.

Accordingly, applicants respectfully disagree with the aforesaid rejection. Because the claims are directed to particular probes rather than any probe from the LTR region in general, the combination of **Montagnier** with **Research Genetics** does not

teach all the elements of the claims, and does not render the claimed invention *prima facie* obvious.

Montagnier et al. is mainly focused on the identification and determination of HIV-1 derived polypeptides. The part of the patent that discusses amplification (by the PCR method) of DNA or RNA, is a side issue thereof. The Examiner refers to Column 19, last paragraph bridging to column 20, first two lines of Montagnier, arguing that this paragraph teaches explicitly that primers should be directed to conserved regions and that just such a region can be found in the LTR. However, please note:

1) In the portion of Montagnier et al. to which the Examiner refers, PCR amplification is not discussed as a diagnostic tool *per se*, but as an aid to detect HIV DNA in patients of which the serological status has already been determined.

2) Montagnier et al. does refer to conserved regions, but mentions not only the LTR region but also other conserved regions such as the qao and env regions of HIV-1. Thus the regions from which Montagnier et al. invites selection to be made are considerably larger than the regions recited in the instant claims.

3) Above all, Montagnier makes it very clear that the single primer pair PCR amplification method is NOT considered to be a reliable diagnostic procedure. Indeed, at column 19, second paragraph, it is stated that the HIV-1 antibody status of patients can initially be determined by ELISA techniques and subsequently confirmed by Western blots. Montagnier is suggesting the PCR amplification for further confirmatory testing only. In the last paragraph of column 19, it is stated:

> Since a patient may have been infected with HIV-1 containing genetic variations or deletions in the regions targeted for amplification, the PCR technique using a single primer pair may not produce reliable results. Specifically such variation could result in inefficient primer or probe binding, or elimination of specific endonuclease sites, or both of these problems. For reasons the PCR technique is **preferably carried out with several primer pairs and probes derived from highly conserved regions** of the viral genome...

Clearly the person of ordinary skill in the art would not arrive at the invention defined by the claims of the instant application. It is respectfully submitted that, a single primer pair that effectively can be used to diagnose HIV infections even without a preceding pre-screening process is even **more inventive** in view of Montagnier, because this reference essentially discourages the use of a single primer pair.

With respect to **Research Genetics,** the design program described therein can only be used to find, in a selected sequence, those primer sequences that fulfill the criteria indicated by the user. In other words, one has first to introduce or "feed the computer" with inventive criteria in order for the program to look and search for suitable sequences meeting those criteria.

To expedite clarification of the issues, if the Examiner is aware of more capabilities that are provided by the Research Genetics program than is the instant applicant, then the Examiner is respectfully requested to make of record appropriate evidence indicating all the capabilities of the prior art that is being cited.

As discussed in response to previous citations of this reference, the **user** of the program must make this selection of the target sequence first. Depending on the length of the target sequence (of limited length or longer), the program will eventually provide a great amount of possible primers or, may be, a more limited amount. Nevertheless, **the actual selection of the primer pair** is still to be done by the person using the program on the basis of his own feelings, personal skills, knowledge and luck.

Besides the length of target sequence, the **user** must also decide other issues as well. For example, the minimal and maximal length of the amplified sequence, the minimal and maximal lengths of the primers, the range of melting temperatures that the user considers tolerable, the GC content of the primers, etc., are all issues to be considered. Based upon the selections by the user, the program will come up with sometimes even a large number of possible primers. The program cannot "predict" which primer pair is a good one and which one gives only a poor performance. The program cannot select a good primer pair; it can only carry out the instructions that are keyed in by the user.

Furthermore, in addition to being very sensitive (the primer pair should be able to allow effective amplification even if the target sequence is only present in minute amounts in the starting material), the primer pair should not react at all with any other sequence (which would result in false positive test results).

Moreover, the primer pair should, although being selective, still react with as many different HIV isolates as possible. Amongst different HIV isolates there is some sequence variation. The primers should, of course, be able to amplify nucleic acid from all HIV variants or mutations, otherwise HIV positive samples may be missed by the test. Thus, for a diagnostic test kit that is supposed to be able to detect each and every variant of HIV, the program has no predictive value whatsoever.

Thus, even in the unlikely event that a skilled person designing a diagnostic kit would use the program to select suitable HIV primers, the selection of the primers would be dependent on decisions taken by the skilled person and not by the software constituting the program.

As supporting evidence of nonobviousness, enclosed herewith is a further literature reference by **DeBaar et al.** (J. of Clin. Microbiol., 1999, 37(6)), pp. 1813-1818). This references describes that the design of the primer pair according to the invention resulted in a specific and sensitive assay, which was the first able to quantify both group M and O viruses. It is respectfully submitted that a novel assay in accordance with the present invention would not rise to the level of a publication a peer review publication such as this if it were *prima facie* obvious to persons of ordinary skill in the art. Applicants will be pleased to submit this reference or this information in the form of a supplemental information disclosure statement or a Rule 132 Declaration, if the examiner deems that this would help facilitate allowance of the instant application.

In any case, it is respectfully submitted that this application is in condition for allowance, which action is respectfully requested.

Respectfully submitted,

Kenneth D. Sibley
Registration No. 31,665

USPTO Customer No. 20792
Myers Bigel Sibley & Sajovec
Post Office Box 37428
Raleigh, North Carolina 27627
Telephone (919) 854-1400
Facsimile (919) 854-1401

Enclosure: **DeBaar et al.**

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231, on June 13, 2001.

Vickie Diane Prior
Date of Signature: June 13, 2001